Does increasing blood pH stimulate protein synthesis in dialysis patients?

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Abstract: BACKGROUND: Although the mechanism of muscle wasting in end-stage renal disease is not fully understood, there is increasing evidence that acidosis induces muscle protein degradation and could therefore contribute to the loss of muscle protein stores of patients on hemodialysis, a prototypical state of chronic metabolic acidosis (CMA). Because body protein mass is controlled by the balance between synthesis and degradation, protein loss can occur as result of either increased breakdown, impaired synthesis, or both. Correction of acidosis may therefore help to maintain muscle mass and improve the health of patients with CMA. We evaluated whether alkalizing patients on hemodialysis might have a positive effect on protein synthesis and on nutritional parameters. METHODS: Eight chronic hemodialysis patients were treated daily with oral sodium bicarbonate (NaHCO(3)) supplementation for 10-14 days, yielding a pre-dialytic plasma bicarbonate concentration of 28.6 +/-1.6 mmol/l. The fractional synthesis rates (FSR) of muscle protein and albumin were obtained by the L-[(2)H(5)ring]phenylalanine flooding technique. RESULTS: Oral NaHCO(3)supplementation induced a significant increase in serum bicarbonate (21.5 +/- 3.4 vs. 28.6 +/- 1.6 mmol/l; p = 0.018) and blood pH (7.41 vs. 7.46; p = 0.041). The FSR of muscle protein and the FSR of albumin did not change significantly (muscle protein: 2.1 +/- 0.2 vs. 2.0 +/- 0.5% per day, p = 0.39; albumin: 8.3 +/- 2.2 vs. 8.6 +/- 2.5% per day, p = 0.31). Plasma concentrations of insulin-like growth factor 1 decreased significantly (33.4 +/- 21.3 vs. 25.4 +/- 12.3 nmol/l; p = 0.028), whereas thyroid-stimulating hormone, free thyroxin and free triiodothyronine did not change significantly and nutritional parameters showed no improvement. CONCLUSION: In contrast to other findings, raising the blood pH of dialysis patients was not associated with a positive effect on albumin and muscle protein synthesis, or nutritional and endocrinal parameters.

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Does Increasing Blood pH Stimulate Protein Synthesis in Dialysis Patients?

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Key Words
Protein synthesis · Hemodialysis · Metabolic acidosis · Sodium bicarbonate · Thyroid hormones · Insulin-like growth factor 1

Abstract
Background: Although the mechanism of muscle wasting in end-stage renal disease is not fully understood, there is increasing evidence that acidosis induces muscle protein degradation and could therefore contribute to the loss of muscle protein stores of patients on hemodialysis, a prototypical state of chronic metabolic acidosis (CMA). Because body protein mass is controlled by the balance between synthesis and degradation, protein loss can occur as result of either increased breakdown, impaired synthesis, or both. Correction of acidosis may therefore help to maintain muscle mass and improve the health of patients with CMA. We evaluated whether alkalizing patients on hemodialysis might have a positive effect on protein synthesis and on nutritional parameters. ***Methods:*** Eight chronic hemodialysis patients were treated daily with oral sodium bicarbonate ($NaHCO_3$) supplementation for 10–14 days, yielding a pre-dialytic plasma bicarbonate concentration of 28.6 ±1.6 mmol/l. The fractional synthesis rates (FSR) of muscle protein and albumin were obtained by the L-[$^2H_5$ring]phenylalanine flooding technique. ***Results:*** Oral $NaHCO_3$ supplementation induced a significant increase in serum bicarbonate (21.5 ± 3.4 vs. 28.6 ± 1.6 mmol/l; p = 0.018) and blood pH (7.41 vs. 7.46; p = 0.041). The FSR of muscle protein and the FSR of albumin did not change significantly (muscle protein: 2.1 ± 0.2 vs. 2.0 ± 0.5% per day, p = 0.39; albumin: 8.3 ± 2.2 vs. 8.6 ± 2.5% per day, p = 0.31). Plasma concentrations of insulin-like growth factor 1 decreased significantly (33.4 ± 21.3 vs. 25.4 ± 12.3 nmol/l; p = 0.028), whereas thyroid-stimulating hormone, free thyroxin and free triiodothyronine did not change significantly and nutritional parameters showed no improvement. ***Conclusion:*** In contrast to other findings, raising the blood pH of dialysis patients was not associated with a positive effect on albumin and muscle protein synthesis, or nutritional and endocrinal parameters.

Introduction

Many patients with chronic kidney disease (CKD) display body protein wasting, and often remain wasted despite dialysis [1, 2]. Depending on the method of assess-

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ment of catabolic factors, wasting has been observed in up to 70% of patients on hemodialysis (HD) and in 18–56% of patients undergoing continuous ambulatory peritoneal dialysis (CAPD) [3]. The assessment was based on a combination of clinical, biophysical and biochemical parameters. Serum albumin concentrations <40 g/I are associated with higher mortality rates than concentrations >40 g/I [3, 4]. Prealbumin may also predict mortality in both CAPD and HD patients [5–7].

Although low serum proteins and muscle wasting in HD patients have often been attributed to malnutrition (i.e. an inadequate protein and energy intake), recent evidence suggests that malnutrition is not the principal cause. Other factors, such as inflammation and/or resistance to anabolic hormones, may also interfere with control of the protein balance [2]. In addition, several studies suggest that metabolic acidosis represents a major stimulus for protein degradation and muscle wasting in CKD patients. Metabolic acidosis resulting from the impaired excretion of non-volatile organic acids and reduced renal synthesis of bicarbonate accompanies both acute and chronic renal failure [8, 9]. Despite HD with a high bicarbonate buffer of 35 mmol/l, a significant number of patients remain acidotic [10].

Attempts to reduce protein degradation and/or increase protein synthesis, and thus improve nitrogen retention, are important for the development of strategies to counteract muscle wasting and to improve protein homeostasis and survival in catabolic diseases (e.g. sepsis, renal and liver failure, HIV, cancer, anorexia and starvation). However, the mechanisms of muscle protein wasting in different catabolic processes are complex and poorly understood.

The important role of metabolic acidosis in the development of protein degradation is indicated by the fact that correction of acidosis induces normal growth in children with renal tubular acidosis [11] and leads to downregulation of ubiquitin mRNA in CAPD patients. Activation of the intracellular ATP-dependant ubiquitin proteasome pathway is one of the most important mechanisms for protein degradation [2, 9, 12, 13]. Moreover, there have been studies examining the impact of metabolic acidosis in human volunteers given ammonium chloride orally. The study of Ballmer et al. [14] confirmed that induced metabolic acidosis causes a negative nitrogen balance and a significant decrease in serum albumin synthesis. Furthermore, Reaich et al. [15] found a significant increase in protein breakdown and amino acid oxidation after the ingestion of NH_4CI for 5 days, findings confirmed by Straumann et al. [16] but not by Nair et al. [17]. In addition, a depression in muscle protein synthesis was observed after 2 days of metabolic acidosis in humans [18] and after 1 day in rats [19, 20]. However, prior studies had failed to detect a response in protein synthesis [21, 22].

Body protein homeostasis depends on the balance between synthesis and degradation. Because proteins are continually degraded and synthesized, protein loss can occur as result of either increasing the breakdown, decreasing the synthesis, or both.

The inhibition of protein synthesis by acidosis poses the logical question of whether alkalosis reverses this effect and stimulates protein synthesis.

More recent studies have come to the conclusion that muscle protein synthesis is inhibited by acidosis and may also be stimulated by alkalosis [23]. Thus, correction of acidosis in non-dialysed patients with CKD improves the nitrogen balance [24, 25]. In a study with 18 non-dialysed patients 6 months after oral supplementation with sodium bicarbonate ($NaHCO_3$), Verove et al. [26] found an increase in serum albumin and prealbumin concentrations and a decrease in the protein catabolic rate. Patients on HD after 3 months of correction of metabolic acidosis showed an increase in their albumin concentrations and an improvement in protein catabolic rates [27]. However, the study of Brady and Hasbargen [4] did not show any benefit of raising the pre-dialysis bicarbonate from 17 to 20 mmol/l. More direct evidence for a role of alkalosis was observed in a study of intensive care patients, in whom hyperventilation, involving respiratory alkalosis, stimulated muscle protein synthesis [28]. Increasing bicarbonate concentration has also been shown to correct insulin-like growth factor 1 (IGF-1) levels, improve growth hormone sensitivity and normalize free triiodothyronine (T_3) [29].

The aim of the study is therefore to investigate whether increasing the serum pH and bicarbonate concentration in patients with chronic metabolic acidosis (CMA) would reverse IGF-1 and thyroid alterations, improve catabolic status and enhance protein synthesis.

Methods

Subjects

Eight uremic patients (7 males and 1 female, mean age: 58 ±15 years, serum urea: 20.5 ± 4.9 mmol/l; serum creatinine: 869.1 ± 236.7 μmol/l), who had been on regular HD thrice weekly for at least 1 year, were recruited for the study. The main demographic and renal disease characteristics are shown in table 1. Inclusion criteria were as follows: mean pre-dialysis serum bicarbonate <18 mmol/l on 1 measurement during the last 3 months and a clinically stable condition. Patients on oral supplementation with

$NaHCO_3$, with cancer, systemic inflammatory disease, chronic liver disease or severe wasting (BMI <15, body weight loss in 3 months >10%) were excluded. The study was approved by the local ethics committee of the Kantonsspital Winterthur, Switzerland. All patients gave written informed consent.

Preliminary Study

The pre-study was performed with the aim of determining the dose of $NaHCO_3$ required to increase the blood HCO_3 concentration above 25 mmol/l. Six of the patients of the main study were placed on oral supplementation with $NaHCO_3$ for 2 weeks. Each tablet contained 7.7 mEq of HCO_3, and each patient received 1 mEq/kg dry weight/day of bicarbonate, rounded to the nearest tablet and divided into 3 doses. To optimize the over-correction procedure, the required dose of $NaHCO_3$ was adjusted according to the plasma HCO_3 concentration measured before each dialysis session.

Measurement of Muscle Protein Synthesis Rate

Protein synthesis rates were measured with the flooding method, as described previously [18]. Before the dialysis session and after an overnight fast, 0.043 g/kg body [$^2H_5$ring]phenylalanine (Tracer Technologies, Sommerville, Mass., USA), with an isotopic enrichment of 7.5 atom% in the first measurement (visit A) and 15 atom% in the second measurement (visit B), was intravenously infused in the arm opposite the arteriovenous fistula (AV fistula) over 10 min.

[$^2H_5$ring]Phenylalanine was mixed with unlabeled L-phenylalanine (Merck, Darmstadt, Germany) in 0.45% NaCl. The sterile solution was prepared by the hospital pharmacy. Blood samples were drawn from the AV fistula at 0, 5, 10, 15, 20, 30, 50 and 90 min. The total blood loss per measurement was about 150 ml. At 90 min, a percutaneous muscle biopsy of about 50 mg was taken from the vastus lateralis under local anaesthesia by means of a biopsy gun (first measurement, visit A). For the second measurement of protein synthesis (visit B), an additional muscle biopsy was taken at time point zero, for determining the baseline enrichment. Plasma and muscle samples were immediately frozen in liquid N_2 and stored at –70°C until further analysis.

Measurement of Albumin Synthesis Rate

After thawing the plasma, albumin was isolated by ethanol extraction from trichloroacetic acid-precipitated plasma proteins, as described previously [30–34]. In every subject, the purity of the albumin isolates was checked by sodium dodecylsulphate gel electrophoresis and compared with a human albumin standard (Sigma, Poole, UK). All isolates presented as a single band corresponding to human albumin. After repeat washes with 2% perchloric acid, the albumin was hydrolyzed in 6 mol HCl for 24 h at 105°C. The hydrolysates were purified by washing with distilled water and then dried in a stream of N_2.

Patients were instructed to maintain their usual diet and activities throughout the study. Medication and dialysis prescriptions were not changed. All patients were dialysed 3 times weekly at a dialysate bicarbonate concentration of 30 mmol/l.

Calculation of Protein Synthesis Rates

Muscle protein synthesis was calculated as the fractional synthesis rate (FSR) expressed as percent per day. FSR was calculated by dividing the increase in L-[$^2H_5$ring]phenylalanine enrichment in muscle protein ($P_2 - P_1$) between 0 and 90 min by the area (A) under the curve of free phenylalanine (precursor) enrichment [14, 18, 30].

$$FSR = (P_2 - P_1) \times 100/A$$

The FSR of albumin was also calculated as described above. FSR of albumin results from the increase in phenylalanine enrichment in albumin between 50 (P_1) and 90 (P_2) min by the corresponding area under the curve of free phenylalanine enrichment.

Body Composition Analysis

Body impedance analysis was performed between 07.00 and 07.30 h (after measurement of protein synthesis and before the HD session). Resistance and reactance were used to calculate body water, fat, and fat-free mass.

Biochemical Blood Parameters

Albumin, prealbumin and transferrin concentrations were measured before the measurement of protein synthesis by bromcresol purple. Plasma acid-base analysis was performed in AV fistula blood samples (Radiometer ABL system 652 Blood Gas Analyzer, Radiometer, Copenhagen, Denmark).

Plasma concentrations of total IGF-1, free thyroxin (fT_4), free triiodothyronine (fT_3) and thyroid-stimulating hormone (TSH) were measured by standard radioimmunoassay methods [14, 18].

Statistics

Statistical comparisons were performed by Student's paired t test. Values of $p < 0.05$ were considered significant.

Table 1. Patients' characteristics at time of entry into study

Subject No.	Sex	Age years	Weight kg	pH	HCO_3 mmol/l	Cause of chronic renal failure
1	M	29	84.5	7.37	18.4	hypertension
2	M	49	77.5	7.41	16.3	unknown
3	M	51	51.5	7.45	24.4	glomerulonephritis
4	M	69	74.0	7.39	21.5	diabetes mellitus, hypertension
5	M	59	75.5	7.44	23.7	diabetes mellitus, hypertension
6	F	61	47.0	7.42	25.1	unknown
7	M	79	71.5	7.42	19.4	obstructive uropathy
8	M	66	72.5	7.40	23.1	glomerulonephritis

Results

Eight patients completed the study (7 men, 1 woman). One patient (No. 4) failed to show an increase in serum bicarbonate after oral $NaHCO_3$ supplementation, due to

Table 2. Blood pH, bicarbonate, sodium, blood urea nitrogen and creatinine before (A) and after (B) $NaHCO_3$ supplementation

Subject No.	Weight, kg		pH		HCO_3, mmol/l		Sodium, mmol/l		BUN, mmol/l		Creatinine, μmol/l	
	A	B	A	B	A	B	A	B	A	B	A	B
1	88.9	91.3	7.37	7.50	18.4	28	134	137	25.8	20.7	1,253	1,069.7
2	82	82.3	7.41	7.44	16.3	27	135	140	25.8	23.5	999.6	970.4
3	53.3	53.7	7.45	7.54	24.4	29.2	141	141	21.0	19.8	706	664.4
5	77.8	79.3	7.44	7.41	23.7	29.3	137	138	20.0	20.9	988.4	946.2
6	47.7	49.2	7.42	7.45	25.1	28.9	134	136	13.6	13.0	530	486.1
7	72.4	73	7.42	7.49	19.4	26.6	136	138	22.7	17.2	743.1	678.9
8	73.8	73.5	7.40	7.45	23.1	31.2	137	139	14.4	17.0	863.6	832.6
Means ± SE	70.8 ± 15.0	71.8 ± 15.2*	7.41	7.46*	21.5 ± 3.4	28.6 ± 1.6*	136.3 ± 2.4	138.4 ± 1.7*	20.5 ± 4.9	18.8 ± 3.4	869.1 ± 236.7	806.9 ± 206.3*

BUN = Blood urea nitrogen. * $p < 0.05$.

Table 3. FSR of albumin and muscle protein before (A) and after (B) $NaHCO_3$ supplementation

Subject No.	Albumin FSR % per day		Muscle protein FSR % per day	
	A	B	A	B
1	8.15	9.62	2.40	2.37
2	7.05	6.92	2.28	1.83
3	8.90	5.94	1.90	2.2
5	11.90	12.97	2.07	1.18
6	9.94	10.42	2.10	2.59
7	5.55	7.09	2.48	2.16
8	6.6	7.47	1.85	1.82
Means ± SE	8.3 ± 2.2	8.6 ± 2.5	2.1 ± 0.2	2.0 ± 0.5
	$p = 0.31$		$p = 0.39$	

poor adherence to the protocol, and was therefore excluded from the analysis. The average patient age was 58 years old (range 29–78 years). Six patients were of normal body composition, with an average BMI of 24.8 ± 3.25, and 1 patient (No. 6) had a BMI of 17. Oral supplementation with $NaHCO_3$ induced increases in plasma bicarbonate, pH and sodium. The bicarbonate of arterialized blood increased from 21.5 ± 3.4 to 28.6 ± 1.6 mmol/l ($p = 0.018$), pH from 7.41 to 7.46 ($p = 0.041$) and sodium from 136.3 ± 2.4 to 138.4 ± 1.7 mmol/l ($p = 0.026$). The body weight increased from 70.8 ± 15 to 71.8 ± 15.2 kg ($p = 0.034$) (table 2).

The FSR of muscle protein did not change significantly after treatment with $NaHCO_3$ (2.1 ± 0.2 vs. 2.0 ± 0.5% per day; $p = 0.39$), neither did the FSR of plasma albumin (8.3 ± 2.2 vs. 8.6 ± 2.5% per day; $p = 0.31$) (table 3).

Serum concentrations of TSH, fT_4 and fT_3 also did not change significantly. Circulating plasma concentrations of IGF-1 before dialysis were in the normal range, but decreased significantly after bicarbonate supplementation (33.4 ± 21.3 vs. 25.4 ± 12.3 nmol/l; $p = 0.028$) (table 4).

The treatment with oral $NaHCO_3$ did not change plasma concentrations of the commonly used biochemical parameters of nutritional status: prealbumin (393 ± 64.5 vs. 377.6 ± 46.9 mg/l; $p = 0.17$), plasma protein (69.7 ± 4.0 vs. 69.3 ± 2.6 g/l; $p = 0.49$), albumin (37.9 ± 4.2 vs. 38.3 ± 2.8 g/l; $p = 0.73$) and transferrin (21.3 ± 4.6 vs. 22.1 ± 2.6 μmol/l; $p = 0.46$) (table 5).

Body impedance analysis could be completed in 6 subjects (patient No. 1 missed the measurement at visit A). The extracellular mass/body cellular mass index did not change significantly (0.85 vs. 0.89 kg; $p = 0.9$), due to a decrease in body cellular mass (0.7 kg) and an increase in extracellular mass (1.6 kg). Lean body mass increased, but not significantly, by 0.9 kg ($p = 0.34$). The total body water increased minimally (0.6 l), and phase angle, volume overflow and sodium did not change significantly (pre-dialytic weight by +1 kg, and sodium by +2.1 mmol/l after $NaHCO_3$ supplementation; table 2). The extracellular water decreased (19.1 ± 4.6 vs. 18.0 ± 3.6 l). Neither dialysis prescription nor antihypertensive therapy needed adjustment for the sodium load.

Table 4. Plasma concentrations of fT_3, fT_4, TSH and IGF-1 before (A) and after (B) $NaHCO_3$ supplementation

Subject No.	fT_3, nmol/l		fT_4, pmol/l		TSH, mU/l		IGF-1, nmol/l	
	A	B	A	B	A	B	A	B
1	1.5	1.5	9.3	10.4	0.7	0.8	76	46
2	1.7	1.9	10.2	12	0.6	0.7	40	32
3	1.6	1.7	10.5	10.4	1.1	1.0	12	13
5	1.7	1.7	10.8	11.9	1.0	1.1	20	17
6	2.1	2	10	10.7	1.3	1.2	36	32
7	1.6	1.8	10.4	13	1.8	2.7	19	12
8	1.9	1.9	12.2	12	1.0	1.8	31	26
Means ± SE	1.7 ± 0.2	1.8 ± 0.2	10.5 ± 0.9	11.5 ± 1.0	1.1 ± 0.4	1.3 ± 0.7	33.4 ± 21.3	25.4 ± 12.3
			$p < 0.05$				$p < 0.05$	

Table 5. Biochemical parameters before (A) and after (B) $NaHCO_3$ supplementation

Subject No.	Albumin, g/l		Prealbumin, g/l		Transferrin, μmol/l		Protein, g/l	
	A	B	A	B	A	B	A	B
1	45.3	41.1	477	421	28	25	77.1	74.5
2	34.9	36.8	429	408	23	23	65.9	65.8
3	35.5	40.5	328	372	18	20	68.6	72.5
5	41.7	41.5	377	377	26	26	72.7	72.5
6	38.2	38	468	422	20	21	67.7	64.7
7	35.7	34.4	338	289	19	19	69.6	68.2
8	33.8	35.6	334	354	15	21	66.4	66.8
Means ± SE	37.9 ± 4.2	38.3 ± 2.8	393.0 ± 64.5	377.6 ± 46.9	21.3 ± 4.6	22.1 ± 2.6	69.7 ± 4.0	69.3 ± 2.6

Discussion

In this study, we investigated whether increasing the plasma bicarbonate concentration in patients on HD stimulated protein synthesis, improved nutritional status and reversed IGF-1 and thyroid derangements. Eight patients were placed on oral supplementation with $NaHCO_3$ for 2 weeks. At the end of the 2 weeks, measurements of protein synthesis and relevant hormones were made. The results showed that 10–14 days of oral $NaHCO_3$ supplementation did not affect the rates of synthesis of muscle protein and albumin, and that neither body protein status nor thyroid hormone status were altered. However, IGF-1 plasma concentrations decreased significantly.

There is increasing evidence that acidosis influences protein metabolism, not only by enhancing protein degradation, but also by inhibiting protein synthesis [35]. Several studies have demonstrated the substantial influence of pH on whole body protein turnover and muscle protein degradation [14–16, 36, 37], but only a few studies have investigated the impact of pH on muscle protein synthesis in vivo. Garibotto et al. [21] showed, using the arterio-venous difference technique and a constant infusion of L-[^{3}H]phenylalanine, that CKD patients had significantly higher rates of both synthesis and degradation of muscle protein. However, the patients with CDK in that study had a mean bicarbonate concentration of 20 mmol/l [21], and were therefore more comparable to subjects without severe acidosis [38].

In another study with humans, Kleger et al. [18] measured muscle protein synthesis in healthy volunteers after induction of acute metabolic acidosis with NH_4CI. The results showed that protein synthesis was depressed by 2 days of metabolic acidosis.

The more recent data of Caso et al. [38] in adult rats suggest that the suppressive effect of metabolic acidosis

on protein synthesis is mainly specific to skeletal muscle, and does not affect visceral tissues. However, studies on human volunteers have shown that serum albumin synthesis is also depressed in metabolic acidosis [14]. In other studies, correction of metabolic acidosis was shown to normalize growth in children with renal tubular acidosis [11] and improve nitrogen balance in CKD [25].

The benefit of bicarbonate supplementation in patients with metabolic acidosis has been known since 1931 [39]. However, dialysis with a high-normal bicarbonate solution is not sufficient to maintain a normal serum bicarbonate concentration over the complete inter-dialytic period, despite high post-dialysis blood pH [40]. After correction of metabolic acidosis with oral bicarbonate supplementation, a decrease in protein degradation was observed by Reaich et al. [25] and confirmed by Graham et al. [41]. This evidence suggests that over-correction of acidosis might improve body protein status of patients on hemodialysis. However, when patients were exposed to different levels of bicarbonate, catabolic parameters, such as serum albumin and skin folds thickness, improved in some [27, 42] but not in all studies [4, 43, 44].

A recent study by Bossola et al. [45] failed to show an effect on nutritional status of HD patients after long-term bicarbonate supplementation at the dose of 1 g thrice daily.

The present study did not show, as expected, a significant improvement in total protein and albumin, but also prealbumin and transferrin plasma concentrations did not change. Moreover, no significant changes were recorded in the FSR of albumin and muscle protein, in agreement with the data of Reaich et al. [25] and Graham et al. [41] with 4 weeks on bicarbonate. However, in the study of Vosswinkel et al. [28], involving intensive-care patients, the same increase in pH (from 7.4 to 7.5) as in the present study induced a significant increase in muscle protein synthesis. The notable difference is that the previous study induced changes in pH by respiratory means, whereas the present study induced metabolic alkalosis. In animal studies, however, respiratory acidosis and metabolic acidosis result in very similar depressions in muscle protein synthesis [19, 20, 46]. It is not clear, therefore, whether the failure to demonstrate an improvement in protein synthesis in the present study may be related to the method of over-correction of acidosis or to other factors. A potential explanation of this lack of effect of alkalinization may be the selection of the subjects; lean body mass, albumin and prealbumin of our patients did not reflect the abnormalities generally attributed to wasted patients. Another consideration is the lack of acidosis at the beginning of the study, although at the time of recruitment the patients had had lower plasma bicarbonate, as required in the inclusion criteria.

Putative hormonal mechanisms involved in the acidosis-induced downregulation of albumin synthesis were also investigated. Growth hormone, IGF-1, insulin and thyroid hormones are, together with cortisol, the most important hormones regulating protein synthesis and degradation [14, 18]. Uremic patients often show laboratory findings suggestive of hypothyroidism, such as a low concentration of peripheral hormones and a blunted TSH response to thyrotropin-releasing hormone [18, 29]. The most evident abnormality is the reduction in fT_3, due to the decreased conversion of T_4 to T_3 by inhibition of 5′-deiodinase [47, 48]. Observations in healthy subjects after induction of metabolic acidosis indicated a mechanism at the level of the thyroid rather than a central inhibitory effect [49]. After correction of CMA or successful renal transplantation, the thyroid function improved progressively, with the circulating hormones reaching normal concentrations [29, 50]. The present findings (low T_3, low T_4 and low but still normal TSH levels) are consistent with thyroid dysfunction, which has been observed in CMA. However, the study failed to confirm a significant improvement after oral $NaHCO_3$ supplementation. A possible explanation for this failure is the short intervention period compared to other studies, i.e. after renal transplantation, thyroid hormones reach normal concentrations only after 8 days to 1 month [50].

In human volunteers, IGF-1 inhibits protein degradation and stimulates protein synthesis [51, 52]. Experimental studies with healthy humans showed that induced chronic but not acute metabolic acidosis reduced plasma IGF-1 concentrations due to peripheral insensitivity to growth hormone [14, 18, 29]. In contrast, non-malnourished patients on HD have serum IGF-1 concentrations that are similar or higher compared to subjects with normal renal function [53–57]. However, intracellular IGF-1 in the muscle has been shown to be markedly reduced [57]. Recent observations have shown that correction of acidosis by oral citrate administration partially corrected the IGF-1 plasma concentrations and reversed growth hormone insensitivity [29].

In the present patients, the pre-dialysis high IGF-1 concentrations decreased to 70% after 10 days on oral $NaHCO_3$ supplementation. This suggests that over-correction may have an adverse effect on IGF-1 and that a mechanism other than acidosis must be responsible for reduction of circulating IGF-1 levels.

There are several limitations to our study. First, the number of patients was very low and significant changes might have been missed. Also, the observation period and supplementation were rather short, so that we may have missed a profound effect. However, depressions in muscle protein synthesis were already observed after 2 days of induced metabolic acidosis in humans [3] and after 1 day in rats [4, 5] in previous studies.

A further limitation may be the good quality of dialysis in our patients. Many patients fulfilling the inclusion criterion of a pre-dialysis serum bicarbonate <18 mmol/l within the last 3 months, showed a normal blood pH at the start of the study. It is therefore quite possible that the expected effect on albumin and muscle protein synthesis might only occur when the pH is below 7.4. Although the patients were instructed to maintain their usual diet and activities, we did not measure protein catabolic rate and Kt/v to assess dietary protein intake and dialysis adequacy.

In conclusion, we find that raising the pH in HD patients is not associated with a positive effect on protein synthesis, catabolic parameters or endocrine derangement.

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